NATIONAL PHARMACEUTICAL ALLIANCE

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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Docket # 99D 2635

Gentlemen:

Attached are two copies of the National Pharmaceutical Alliance's Technical Committee's comments on the draft Guidance for Industry; ANDAs: Blend Uniformity Analysis Today is the closing date for comments. We appreciate the opportunity to comment.

Very truly yours,

Robert A. Jenusi for

Christina Sizemore
President

99D-2635

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National Pharmaceutical Alliance's Technical Committee Comments on the Guidance for Industry, ANDAs: Blend Uniformity Analysis, Docket Number 99D-2635

NPA's Technical Committee welcomes and is grateful for the opportunity to comment on this draft guidance. Our comments follow:

1. It is our opinion that this guidance and its contents, blend uniformity analysis (BUA), are not needed after a manufacturing process has been validated. Unfortunately, although this is described as a draft, its content has been practiced on ANDA submissions for over a year apparently having been put in place as policy by the Office of Generic Drugs without input from the generic industry. In general, blend uniformity analysis for each production batch is redundant when coupled with process validation, finished goods content uniformity analysis, and finished goods assay analysis. In practice, BUA becomes a process validation exercise for every lot of drug product produced. This is expensive, time consuming and lends no additional value as a control on the quality of the finished drug product.

2. BUA has a useful purpose during the validation of a process, not during the routine manufacture of a drug product. Also, because BUA has, at times, a flawed sampling procedure, out of specification results are suspect. FDA is simply increasing the already sizeable regulatory burden companies face by insisting on this test for every batch.

3. Current sampling technology does not universally allow the consistent collection of unit dose samples representative of the powder blend. It is generally recognized that the sampling thief or spear is far from an ideal sampling device due to its propensity to provide non-representative samples. Since sampling errors can be influenced by the design of the thief, sampling technique, and the physiochemical properties of the blend, difficulty in applying unit dose sampling to blend uniformity validation could render the data meaningless.

The fact that there is no second tier or end product testing (content uniformity) if good BUA is not obtained makes this guidance completely unacceptable since blends which may be perfectly good will have to be discarded when they do not meet the specifications imposed by this guidance. This will add both a dollar and environmental cost to the guidance.

OGD personnel have resisted content uniformity testing as a second test when BUA cannot be obtained for whatever reason. The major concern seems to be that the normal USP content uniformity test <905> uses only 30 units from a batch of 1 million or more tablets or capsules. However, this can be overcome by specifying more samples when poor BUA results are obtained.

4. The guidance includes numerous references to GMPs in the discussion of the requirements for BUA. We do not believe that blend uniformity analysis in general, or as described in this guidance, is required for a process to be in accord with GMPs. [redacted]

[redacted] Additionally, literally hundreds of drug products are now on the market by our member firms after having been manufactured without BUA in plants and via procedures that have been found by FDA to be operative under GMPs. The latter has been true for years. In light of this background, the guidance makes no contribution to GMPs or to drug products being produced in the United States by our member firms today. In fact, it forces the introduction of a test which is, at best, of limited value.

One reference in the draft guidance to GMPs on page 1 is to 21 CFR § 211.110(a)(3) which the guidance claims is an "in-process testing requirement for adequacy of mixing to assure uniformity and homogeneity." Actually, 211.110(a) lists five "control procedures" that may be used "where appropriate". FDA has deleted the last phrase in its reference. There are many persons both within the Agency and outside it that feel BUA is not an appropriate in-process test. The term "as appropriate" is also used in 211.110(c) when referring to the testing of in-process materials. Additionally, two of the five tests mentioned in the referenced section of the GMP regulations, tablet or capsule weight variation and dissolution time and rate must be measured on the dosage form not the blend.

5. There are many ways to assure compliance with GMPs. One is by validating the production process. Once the latter has been accomplished, extra in-process tests that may have been used for validation may be discontinued. One of these is BUA. Blend mixing time is a useful in-process control to assure the proper blend composition after it is used with BUA during development and validation.

6. Blending may continue during the manufacturing process after the blending step, e.g., in discharge into drums, in the movement of drums and in the hopper of the tableting or encapsulating machines. Thus, measuring blend uniformity before these steps may have little relationship to the blend that is tableted or encapsulated.

Recommendation

In light of the above six points, we recommend that this draft be abandoned. We also recommend that the current implementation of the OGD policy on BUA also be abandoned and that the Agency wait until the results from the PQRI initiative on this topic are available before making a decision on BUA for every manufactured batch of drug tablet or capsule product. After the PQRI data become available, some kind of workshop may be useful.

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